IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Bill H. McAnalley, et al.	§	Attorney Docket No. 23100.36
Serial No.: 09/242,215	§	Confirmation No. 9780
Filed: February 8, 1999	§	Customer No. 27683
For: COMPOSITIONS OF PLANT CARBOHYDRATES AS DIETARY SUPPLEMENTS	§	Group Art Unit: 1654
	§	Examiner: M. Flood

DECLARATION UNDER RULE 37 C.F.R. § 1.132

1. My name is Thomas H. Gardiner. I received a B.A. degree in biology in 1968, a M.S. degree in pharmacology in 1970, and a Ph.D. degree in pharmacology in 1972 all from the University of Missouri.

2. Since 1970 I have worked continually in the fields of pharmacology and toxicology, with specialization in the absorption, distribution, metabolism, and excretion (ADME) of natural and synthetic chemicals and nutrients.

3. Since 1999 I have been the president of Gardiner & Associates, Inc., a regulatory, pharmacology, toxicology, and glycobiology consulting company that provides scientific and regulatory expertise to industrial clients involved with chemical manufacture and nutritional supplements. During that time, I have evaluated over 4,000 peer-reviewed scientific publications on nutritional supplements and authored numerous critical scientific reviews involving the ADME and biological activities of glyconutrients.

4. I retired from Shell Chemical Company in 1999 after 20 years of service as a research and regulatory toxicologist and global product steward, with responsibilities for development and coordination of international research and health, safety, and environmental programs for Shell Group Companies worldwide.

5. Prior to my employment with Shell, I was an Assistant Professor of Pharmacology from 1974-80 at the University of Texas Health Science Center at Dallas, where I conducted NIH-sponsored r search programs concerned with the ADME of chemicals by the lungs.

6. I have authored numerous publications, which are detailed in my Curriculum Vitae, a copy of which is attached.

7. I have read and understand U.S. Patent Application Serial No. 09/242,215 to McAnalley et al. (the "McAnalley Application"), U.S. Patent No. 4,871,557 to Linscott ("Linscott"), U.S. Patent No. 5,021,560 to Montreuil et al. ("Montreuil"), "Analysis of the Isolated Hyaline Layer of Sea Urchin Embryos", Developmental Biology 27, 494-503 (1972) by Citkowitz ("Citkowitz") and U.S. Patent No. 3,947,601 to Ortega ("Ortega").

8. I believe that claims 1, 6-17, 22, 27-36 and 40-43 of the McAnalley Application are directed to an important and patentable improvement over the subject matter described in Linscott, Montreuil, Citkowitz and Ortega.

9. I have reviewed the Office Action from the United States Patent and Trademark Office dated December 18, 2002, in the McAnalley Application. I noted the following statement on page 4, lines 9-12 of the Office Action:

> "[N]owhere in the disclosure of Applicant can be found any teaching or suggestion of a treatment of sources of carbohydrates comprising the claimed saccharides to make the saccharides of the claimed invention bioavailable as monosaccharides."

10. Instead, the McAnalley Application discloses at page 8, lines 19-23 that in an embodiment of the invention disclosed in the McAnalley Application, the compositions:

> "[I]nclude predigested forms of at least one of the eleven essential carbohydrates. This can include one or all of the following: 1) physical digestion such as shearing or treatment with ultrasound, 2) chemical digestion such as enzymatic digestion, and acid or base hydrolysis, and 3) biological digestion with microbes such as bacteria, fungi or molds."

11. Based on my experience with carbohydrate chemistry, the predigestion of carbohydrates such as tragacanth gum and gum ghatti makes the constituent saccharides of such gums bioavailable as monosaccharides. Accordingly, one skilled in the art would have understood that the predigestion of sources of carbohydrates comprising the claimed saccharides would make the saccharides of the claimed invention bioavailable as monosaccharides.

12. I note the following statement on page 7 of the Office Action dated December 18, 2002, in the McAnalley Application:

> [T]he dietary supplement compositions taught by Linscott, which comprise the instantly claimed saccharides inherently must read upon such bioavailable monosaccharides.

13. That statement is incorrect in view of the state of the art as of August 4, 1997. One skilled in the art would *not* have understood that the constituent monosaccharides of Linscott's dietary supplement fiber are inherently bioavailable (usable by the body), since it has been well documented for many years that dietary fiber, which occurs naturally in many foods and dietary supplements, is *not* digestible, and, therefore, the monosaccharides found in the fibers are not bioavailable (ie. usable) (Tungland and Meyer, Comprehensive Reviews in Food Science and Food Safety 3:73-92, 2002, attached as Exhibit A). Since monosaccharides in nature exist as polysaccharides and glycoconjugates (glycoproteins and glycolipids), they have to be hydrolyzed (digested) from the polymers, proteins, or lipids to be released as individual saccharides (Murray, Harper's Biochemistry, Ch. 56, 25:675-694, 2000, attached as Exhibit B and Guyton & Hall, Textbook of Medical Physiology, 10th edition, 2000, pages 754-756, attached as Exhibit C). In fact, dietary fiber (both soluble and insoluble) has traditionally been promoted for its non-digestible properties that make it a good bulking agent to hasten elimination of colon contents, so that there would not have even been a motivation to develop digestible dietary fibers. Therefore, since Linscott did not teach that dietary fibers are predigested to make individual monosaccharides bioavailable, any beneficial effects claimed by Linscott would have to be due to the undigested dietary fibers and not the individual monosaccharides that are contained in the dietary fibers.

14. I note the following statements on page 8 of the Office Action dated December 18, 2002, in the McAnalley Application:

> [T]here is no indication that the constituent saccharides of the glycoprotein taught by Montreuil are not bioavailable as monosaccharides. Furthermore, Applicant has not provided a clear and convincing argument that the constituent saccharides of the glycoprotein taught by Montreuil are not bioavailable as monosaccharides."

15. Those statements are incorrect in view of the state of the art as of August 4, 1997. One skilled in the art would *not* hav understood that the individual monosaccharide residues are even possibly bioavailable as the active components of the glycoprotein, simply because analysis of the glycoprotein showed that the monosaccharide residues were present in the

glycoprotein. Since the monosaccharides are covalently bound to the protein of the glycoprotein, it is a basic mechanism of biochemistry that the glycoprotein itself would have to be predigested, for example, by enzymes that break the covalent bonds in order to release the saccharides to make them bioavailable (Murray, Harper's Biochemistry, Ch. 56, 25:675-694, 2000, attached as Exhibit B). Montreuil describes the use of enzymes in the analysis of the glycoprotein in order to identify its structure and isolate and characterize the individual monosaccharides that comprise the glycoprotein, but Montreuil does not teach that enzymatic (or any other type) predigestion of the glycoprotein is required for the glycoprotein to be immunogenically active. In fact, as of August 4, 1997 hundreds of other biologically active glycoproteins that were intact, and not predigested, were already described in the scientific literature (Kobata, Structures and Functions of the Sugar Chains of Glycoproteins, Eur. J. Biochem, 209, 483-501 (1992), attached as Exhibit D), so that Montreuil would not have even been motivated to predigest the glycoprotein in order to achieve biological activity.

16. I note the following statements on pages 9 and 10 of the Office Action dated December 18, 2002, in the McAnalley Application:

> "The instantly claimed saccharides are intrinsically inherent to the composition taught by Ortega, as evidenced by the teachings of Citkowitz set forth immediately above... As there is no indication that the constituent saccharides of the referenced compositions taught by Citkowitz and Ortega are not bioavailable as monosaccharides and as Applicant has not provided a clear and convincing evidence to suggest otherwise, both of the cited references are deemed to anticipate the claimed subject matter."

17. Those statements are incorrect in view of the state of the art as of August 4, 1997. One skilled in the art would *not* have understood that saccharides identified in sea urchin eggs are bioavailable, simply because they comprise the egg structure. That would be like saying that since rocks contain calcium and other minerals, rocks in the diet would supply those mineral nutrients. By analogy, the monosaccharides in the sea urchin eggs would have to be released in some bioavailable form to be biologically active. Perhaps an even more compelling argument can be made by considering the results of the hyaline layer composition provided on pp. 495-496 of Citkowitz. The author states:

> "According to protein measurements, *the hyaline layer is 100% protein*; however, within the experimental error for protein and dry weight, there is room enough to accommodate the 2 or 3% carbohydrate that is also present." It appears to me, as a qualified peer revi wer, that these data can better be interpreted to indicat that the monosaccharides

existed as part of the protein structure (which the author states comprised 100% of the composition) rather than as free, unbound monosaccharides in the hyaline layer. On that basis, they would not be bioavailable unless the hyaline layer were predigested in some way to release them from their protein entrapment, and there is no indication in Ortega that any predigestion steps were performed. Besides, as a qualified peer reviewer, I would not accept an explanation of data based simply on it being "within experimental error" as stated by Citkowitz.

18. One major distinction of the subject matter of claims 1, 6-17, 22, 27-36 and 40-43 of the McAnalley Application is that the state of the art as of August 4, 1997 was that the subject monosaccharides could be synthesized by the body from dietary glucose, which would obviate a dietary need for bioavailable monosaccharides. There was no motivation prior to the invention described in the McAnalley Application to develop a dietary supplement comprised of individual, bioavailable monosaccharides. In contrast, the invention in the McAnalley Application teaches that bioavailable monosaccharides as dietary supplements are "essential for the production of correctly structured and, therefore, properly functioning glycoproteins". Since the filing of the McAnalley Application, this claim has subsequently been validated by Martin et al. (Biochemie 80:75-86, 1998, attached as Exhibit E) and Alton et al. (Glycobiology 8(3):285-295, 1998, attached as Exhibit F). For example, Martin et al. described the "availability of specific sugars for glycoconjugate biosynthesis" in animals and man. Alton et al. described the "direct utilization of mannose for mammalian glycoprotein biosynthesis". Individual monosaccharides (not glycoproteins or undigestible polysaccharide fibers), which are specifically bioavailable for glycoconjugate biosynthesis, were the subject of these publications. This clearly distinguishes the subject matter of claims 1, 6-17, 22, 27-36 and 40-43 of the McAnalley Application from Linscott, Montreuil, Citkowitz, and Ortega which as noted above do not so much as mention the administration of individual monosaccharides.

19. Another major distinction of the subject matter of claims 1, 6-17, 22, 27-36 and 40-43 of the McAnalley Application from Linscott, Montreuil, Citkowitz and Ortega is that none of the cited references describe the use of predigestion to make the monosaccharides bioavailable. Rather, they describe the use of a glycoprotein, monosaccharide-protein complex, or undigestible polysaccharide fiber, which contains monosaccharides as part of their structure, as the active principle of the invention. The state of the art as of August 4, 1997 and today is that digestion of carbohydrate polymers and protein is essential to make the individual

monosaccharides bioavailable (Guyton & Hall, Textbook of Medical Physiology, 10th edition, 2000, pages 754-756, attached as Exhibit C).

20. I believe that the important disclosures of the references cited by the examiner can be summarized as follows:

The invention by Linscott discloses a food product (ie. granola bar) that provides a convenient and palatable source of supplemental dietary fiber, which has been shown to have important health benefits. Since the state of the art is that dietary fiber (both soluble and insoluble) is undigestible, the invention by Linscott does not provide a dietary source of bioavailable monosaccharides, even though monosaccharides comprise the structure of dietary fibers.

The invention by Montreuil et al. is an immunogenic glycoprotein that, upon structural analysis, is found to contain monosaccharide residues as part of the glycoprotein. The intact glycoprotein, rather than the monosaccharide residues of the glycoprotein, appears to be the biologically active principle of the invention, since there is no teaching in the embodiment of the invention or its claims of predigestion of the glycoprotein prior to its use as an immunogenic agent. The state of the art is that predigestion of the glycoprotein prior to its use with enzymes, for example, would be required to make the glycoprotein monosaccharides bioavailable, since they are covalently bound to protein.

The invention by Ortega discloses a useful food for fish and invertebrates that is made from broken sea urchin eggs. Analysis by Citkowitz of sea urchin embryos (which are the contents of eggs) shows that monosaccharides are present in the embryos, and would therefore be presumed to be present in the broken sea urchin eggs of Ortega's invention. However, it appears that the monosaccharides described by Citkowitz are contained in the protein composition of the embryos, and are not bioavailable. Thus, any monosaccharides that might be present in the broken sea urchin eggs of Ortega's invention would also not be bioavailable, since there is no claim of predigestion of the eggs prior to their use as food. Simply breaking the eggs would not be expected to release entraped monosaccharides any more than breaking rocks would make their min ral contents bioavailable. State of the art teaches that predigestion of protein-monosaccharides with enzym s, for xample, would be required to make them bioavailable, since they are part of th protein structure.

21. Accordingly, I do not believe that any of Linscott, Montreuil, Citkowitz, and Ortega, alone or in combination, discloses or suggests the subject matter of claims 1, 6-17, 22, 27-36 and 40-43 of the McAnalley Application, since none of them disclose or suggest bioavailable monosaccharides that are made bioavailable by predigestion.

I acknowledge that willful false statements are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and may jeopardize the validity of this McAnalley Application or any patent issuing from it. I declare under penalty of perjury under the laws of the United States that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true.

Thomas H. Gardiner

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April 15, 2003

Date

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RESUME

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PROFESSIONAL EXPERIENCE:

1999-Present **Gardiner & Associates, Inc., President**
Consulting in Nutritional Supplements, Pharmacology, Toxicology & Regulatory Affairs

- Nutritional Supplements: Efficacy and safety issues, product development programs, and reviews of scientific literature on biological effects of ingredients
- Pharmacology: Pharmacokinetic study design and interpretation, particularly via the inhalation route, and general pharmacology of drugs and biologically active substances
- Toxicology: General toxicology issues, expert witness in toxic tort litigation, and legal counsel advisor on product stewardship and human health and environment issues
- Regulatory: Regulatory compliance related to product development programs, TSCA and FIFRA requirements for chemical and pesticide registrations, FDA requirements for efficacy and toxicity testing for new drugs, DSHEA requirements for dietary supplements, and regulations governing study conduct, such as Good Laboratory, Clinical, or Manufacturing Practices, and EPA/FDATest Guidelines

1993-1999 **Global Product Steward &**
Regulatory Affairs Coordinator
Shell Chemical Co.

- Global responsibility to develop, implement, monitor, maintain, and coordinate health, safety and environment programs for various domestic and international Royal Dutch/Shell manufacturing facilities
- Lead product stewardship team of business, distribution, manufacturing, and HS&E representatives to conduct site visits of U.S. and non-U.S. customer manufacturing facilities to monitor compliance with Shell HS&E, regulatory and operational standards
- Represent Shell Chemical Co. Resins/Polymers, Solvents, and Phenol Business interests on trade association groups at the Chemical Manufacturers Association (CMA), The Society of the Plastics Industry (SPI), and The Society for Advanced Composite Materials Association (SACMA) in Washington, D.C..
- Chairmanship of isopropanol, phenol, and cumene chemical industry advocacy panels and toxicology technical committees at CMA, co-chairmanship of epichlorohydrin, bis-phenol A,

and epoxy resin advocacy and toxicology groups at SPI, and chairmanship of the Environment, Health & Safety Committee at SACMA.

- Negotiation of TSCA and FIFRA test rule regulatory and science requirements with the EPA and management of industry-sponsored, multi-stakeholder toxicology testing programs at various contract testing laboratories.
- Preparation of CMA chemical industry positions on key scientific and regulatory issues for harmonization both domestically and internationally with regulatory organizations in the U.S., Europe, and Japan with global impact on a variety of TSCA and FIFRA regulated chemicals.
- Worked with various legal, technical, and regulatory consultants, senior EPA staff, and international trade groups to devise practical regulatory/business strategies that are consistent with the diverse regulatory requirements.
- Extensive interaction with Shell Chemical Co. global business managers to determine appropriate strategies consistent with Shell domestic and global business needs and requirements for both new and existing chemical products.
- Product stewardship included preparation of Material Safety Data Sheets (MSDS) and other HS&E literature for approximately 200 Shell Chemical Co. resin, polymer, and chemical intermediate related products.
- Life cycle analysis of major chemical products to assess risk management needs and appropriate environment, health, and safety controls.
- Advise Shell legal counsel and provide expert witness testimony in litigation cases.
- Management of the Suspect Hazard Reporting Network for Shell Oil Co. and its subsidiaries, required under Section 8(e) of TSCA, which involves review of possible workplace hazards and exposures to determine regulatory reporting requirements, and advise senior Shell management on technical and regulatory issues related to both new (TSCA 5) and existing (TSCA 4) chemical products.

1986-1993 **Staff Toxicologist - Head Office**
Health, Safety & Environment
Shell Oil Co. & Subsidiaries

- Managed the corporate toxicology R&D program for Shell Chemical Co. epoxy resins, polymers, and related intermediate chemicals, which included development of testing strategies, budgets, and plans and coordination of extramural contracts for toxicology testing and research.
- Responsible for corporate Quality Assurance Unit required by EPA, FDA, and FIFRA Good Laboratory Practices and development and implementation of relevant QA policies with Shell subsidiaries.
- Chairmanship of toxicology technical committees for phenol, epoxy resins, epichlorohydrin, bisphenol A and composite resins at CMA, SPI, and SACMA trade associations.
- Conducted or reviewed human health risk assessments for Royal Dutch Shell products, reviewed/recommended standards for evaluating possible health risks associated with air toxics and water contaminants, and coordinated HS&E review and comment on Federal guidelines and health risk assessment criteria.
- Technical advise to legal counsel and expert witness testimony in toxic tort litigation.

1980-1986 Supervisor - Staff Research Toxicologist
Toxicology Research Laboratory
Shell Development Co.

- Responsible for line management of 5 support staff (B.S.), 9 contract staff (B.S.), and 8 research staff (Ph.D.), which conducted dermal, oral, eye, and inhalation - acute, subchronic, and chronic toxicity testing for a variety of general toxicity, reproductive, immunotoxicity, and neurotoxicity end-points in laboratory animals.
- Required knowledge of OSHA Hazard Communication requirements, EPA/FDA Good Laboratory Practices, and regulatory toxicology testing requirements.
- Managed the toxicology support function for Shell Chemical Company's Agricultural Chemicals Product Development program, which involved coordination with regulatory experts and business managers to develop testing plans and timelines that met business, marketing, and regulatory requirements.
- Product development and testing strategies were based on a consideration of Acceptable Daily Intakes (ADI) (derived from No Adverse Effect Levels (NOAEL) in animal toxicity tests) vs. product crop residue levels in the desired markets based on efficacy and environmental fate studies.

1974-1980 Assistant Professor in Pharmacology
University of Texas Health Science Center at Dallas

- Research sponsored by NIH grants was conducted and presented at peer-reviewed, scientific meetings and involved the areas of pharmacokinetics, absorption of drugs from the normal and damaged lung, and toxicology of the lung.
- Research responsibilities included Associate Director of Graduate Student Training Program in Pharmacology, coadministrator of NIH interdisciplinary training grant in Pharmacology, Biochemistry and Toxicology (supported 12 graduate student positions), and Principal Investigator on two NIH grants.
- Teaching responsibilities included graduate courses in neuropharmacology and medical student lectures on drug metabolism and pharmacokinetics, supervisory responsibilities for administering the medical student pharmacology teaching laboratories at Southwestern Medical School, and thesis advisor to three graduate students.
- Community service activities involved teaching continuing education courses in pharmacology to practicing nurses and allied health science students.
- Consulting services provided in areas of pharmacology expertise to industrial and EPA clients, and included consulting on FDA regulated drug development projects.
- Expert witness in toxic tort litigation.

EDUCATION:

1972 - Ph.D. (Pharmacology) University of Missouri - Kansas City
1970 - M.S. (Pharmacology) University of Missouri - Kansas City
1968 - B.A. (Biology) University of Missouri - St. Louis

1966 - Associate of Arts (Biology) Jefferson College

TRAINING COURSES:

- Industrial Safety Policies and Procedures
- Industrial Relations Awareness
- Effective Communications
- Basic Management Skills
- Effective Time Management Skills
- Employee Performance Evaluation
- Practical Techniques for Project Management and Cost Control
- Leadership Skills
- Basic Problem Solving
- Advanced Problem Solving

PERSONAL:

- Married, wife is author/novelist
- Four children, 3 grandchildren
- Hobbies include fishing, golf, reading, traveling
- Member of Lions Club, Kiwanis Club, United Way of Hood County, Granbury Brigade
- Community service has included church trustee, saddle club, fireman, EMT, Big Brother

PUBLICATIONS: Available by MEDLINE/TOXLINE published literature search